Use of Antipsychotics in the Treatment of Major Depressive Disorder in the U.S. Department of Veterans Affairs

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Background: Despite the recent U.S. Food and Drug Administration approval of aripiprazole as the first antipsychotic to be used as an adjunct to antidepressant medications in the treatment of major depressive disorder (MDD), information on the current use of antipsychotics in the treatment of MDD has not been available.

Method: Records of antipsychotic prescriptions for all U.S. Department of Veterans Affairs patients diagnosed with MDD (ICD-9 criteria), excluding those with comorbid schizophrenia, schizoaffective disorder, or bipolar disorder, in the fiscal year 2007 (N = 191,522) were examined. Descriptive statistics and generalized estimating equations (GEEs) were used to identify veterans' characteristics, measures of service use, and medical center characteristics that were associated with receipt of these medications and, among such users, with use of the lower doses suggested for MDD.

Results: Altogether, 20.6% of veterans with MDD received antipsychotic medications, and 43% of those who did received them at the higher doses recommended for schizophrenia. GEE models showed that younger age, male gender, psychiatric comorbidities, duration of diagnosed MDD, and more intensive mental health service use were all associated with greater likelihood of receiving antipsychotics and with less likelihood of receiving them at conventional antipsychotic doses.

Conclusion: Antipsychotic medications were commonly used in the treatment of MDD prior to FDA approval, especially in the presence of comorbid mental illness and longer term MDD. Further research is needed to evaluate the long-term safety and efficacy of these medications in combination with antidepressants.

J Clin Psychiatry 2009;70(6):906–912

Received June 6, 2008; accepted July 15, 2008. *From New England Mental Illness Research, Education, and Clinical Center, U.S. Department of Veterans Affairs (VA) Connecticut Health Care System, West Haven, and the Department of Psychiatry, Yale School of Medicine, New Haven, Conn. (Drs. Mohamed and Rosenheck), and the Department of Health Administration and Policy, Medical University of South Carolina, Charleston (Dr. Leslie).*

Conclusions and opinions expressed are those of the authors and do not necessarily reflect the position or policy of the U.S. Department of Veterans Affairs.

Dr. Rosenheck has received research support from Eli Lilly, Janssen, AstraZeneca, and Wyeth; has been a consultant to GlaxoSmithKline, Bristol-Myers Squibb, Organon, and Janssen; and has given expert testimony for the plaintiffs in UFCW Local 1776 and Participating Employers Health and Welfare Fund, et al. versus Eli Lilly and Co; for the respondent in Eli Lilly Canada Inc. versus Novapharm Ltd. and Minister of Health, respondent; and for the Patent Medicines Prices Review Board, Canada, in the matter of Janssen Ortho Inc. and "Risperdal Consta." Drs. Mohamed and Leslie report no financial affiliations or other relationships relevant to the subject of this article.

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In November 2007, the U.S. Food and Drug Administration (FDA) approved aripiprazole as the first antipsychotic to be used as an adjunct to antidepressant medications in the treatment of unresponsive major depressive disorder (MDD) .[1] At almost the same time, a randomized controlled trial was published demonstrating increased significant antidepressant effect from the addition of risperidone to antidepressant monotherapy,[2] perhaps heralding a period of increased use of aripiprazole as well as other second-generation antipsychotics (SGAs) in the treatment of MDD. The magnitude of this increase will largely be determined by the extent of current use of these drugs in MDD, the subject of this study, as well as by their perceived effectiveness and side-effect risks.

According to the World Health Organization, MDD is one of the main causes of disability world wide[3] and is a common illness, with a lifetime risk of about 15% for men and about 30% for women.[4] Lifetime prevalence of psychotic symptoms in MDD patients has been reported to be 14% to 19%,[5,6] and about 20% of patients hospitalized for depression have psychotic features.[7] Data further suggest that 30% of patients with MDD have poor response to antidepressant monotherapy[8] and 25%–45% fail to achieve remission.[9]

Although the addition of aripiprazole to antidepressant treatment at doses of 5–10 mg/day (just below the recommended dose range for schizophrenia) has been shown to improve outcomes in short-term trials, long-term improvements in remission rates have yet to be demonstrated,[10] and there is some evidence that the addition of an SGA to a serotonin reuptake inhibitor (SRI) may be no more effective at 8 or 12 weeks than an SRI alone.[11] Although aripiprazole is the only drug thus far to be approved by the FDA as an adjunctive treatment to antidepressants in MDD, a pending FDA application is on file for quetiapine, and risperidone, olanzapine, quetiapine, aripiprazole, and ziprasidone have all been tested for this purpose and have shown modest evidence of efficacy as augmenting agents, at least in short-term uncontrolled studies.[12–16] Randomized short-term controlled trials with diverse primary endpoints (e.g., rate of relapse, time to relapse, etc.) have shown mixed results.[17,18] Doses of these medications in the treatment of MDD have generally been just below the lower bound of the recommended dose range for treatment of schizophrenia.[19]

The safety profile of antipsychotic agents in patients with MDD also needs to be carefully examined. Any benefit of long-term use of SGAs as augmenting agents for MDD must be weighed against the risk of neurologic side effects (like extrapyramidal symptoms and tardive dyskinesia), hyperprolactinemia, increased weight, and risk of the metabolic syndrome. Although aripiprazole has one of the most favorable metabolic profiles of the atypical antipsychotics, and reports by Berman and colleagues[10] at Bristol-Myers Squibb and Otsuka indicate that addition of aripiprazole to antidepressants for 6 weeks is not associated with "clinically important differences" in metabolic parameters or prolactin levels, there was, however, a median 5% increase from baseline triglyceride levels in those receiving aripiprazole versus no change with placebo and a weight gain of 7% or greater in 5% of those taking aripiprazole versus 1% with placebo. The most common adverse events associated with aripiprazole were akathisia (25% vs. 4% with placebo addition), restlessness (12% vs. 2%), and insomnia (8% vs. 2%).[10]

Of particular importance to this population are studies that have shown increased risk of heart disease among people with MDD.[20,21] Increased metabolic risk associated with long-term use of some SGAs[22,23] may thus be especially hazardous for such patients. Both antidepressants and SGAs are known to be associated with weight gain, which can also contribute to poor compliance.[24–26]

Information on the current use of antipsychotics in the treatment of MDD has not been available. The present pharmacoepidemiologic study uses national data on all antipsychotic prescriptions provided to veterans who received a diagnosis of MDD (ICD-9 criteria) without a comorbid diagnosis of schizophrenia or schizoaffective disorder (ICD-9 295.0) or bipolar disorder (ICD-9 296.0, 296.1, and 296.40–296.89) in the U.S. Department of Veterans Affairs (VA) health care system in fiscal year 2007. We first sought to identify rates of use of antipsychotics in MDD during the period just prior to FDA approval of the first SGA for this purpose, and to examine the proportion of patients who received antipsychotic medication at doses below those recommended by the schizophrenia Patient Outcomes Research Team (PORT) guidelines for antipsychotic therapy of schizophrenia,[19] doses that would appear to be appropriate for treatment of MDD. In addition, we examined specific sociodemographic characteristics and comorbid diagnoses that are associated with the use of these medications, as well as with use at expectable MDD dosages. We further paid specific attention to the use of antipsychotics in the treatment of elderly veterans diagnosed with MDD in 10-year age groups for those aged 45 years and older along with specific characteristics of medical centers (size, emphasis on mental health, and academic emphasis) that may be associated with greater use of this relatively newly approved treatment.

METHOD

Sample and Sources of Data

The sample included all veterans treated at VA medical centers in fiscal year 2007 (Oct. 1, 2006–Sept. 30, 2007) who had at least 1 primary or secondary diagnosis of MDD on at least 1 outpatient encounter or inpatient discharge and who did not receive a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder on any occasion during the fiscal year (N = 191,522). Data on service use and sociodemographic and diagnostic characteristics were derived from national administrative databases. Psychotropic prescription drug records for all antipsychotic agents prescribed to these patients in fiscal year 2007 were obtained from the VA Drug Benefit Management System files. The records of these patients were then merged to compile the database examined for this study.

In addition to the patient characteristics, 3 facility characteristics were also included in the analyses: (1) the size of the facility, (2) emphasis on mental health, and (3) academic emphasis, using measures described in greater detail under Measures. Data describing facility characteristics were taken from the National Mental Health Program Performance Monitoring System, which, in turn, is based on a variety of national VA databases.[27] The institutional review boards of the VA Connecticut Healthcare System and Yale Medical School approved this study.

Measures

For each patient who received a prescription for an antipsychotic medication, the last prescription for an antipsychotic medication filled in fiscal year 2007 was identified as the index prescription. All prescriptions for antipsychotic medications written during the 7 days prior to

the index prescription were then identified. Chlorpromazine equivalents were calculated for each prescription for a conventional antipsychotic medication using updated PORT dosing algorithms.[19] Chlorpromazine equivalents were summed for all conventional antipsychotic prescriptions during the week, including patients receiving more than 1 antipsychotic (24.2%). If the total daily chlorpromazine equivalent for all conventional antipsychotics prescribed during the week was less than the PORT recommendation for schizophrenia of 300 mg chlorpromazine/day, the patient was identified as being dosed at an appropriate MDD dose.

For the SGAs, the total daily dosage for each medication prescribed during the week was calculated. If the total dosage was less than the recommended PORT antipsychotic range, the patient was identified as being dosed appropriately for MDD. SGA doses were also converted to chlorpromazine equivalents by linear extrapolation from the maximum and minimum PORT-recommended doses of both SGA and chlorpromazine.[19] These were used to estimate the chlorpromazine-equivalent total dosage of patients taking more than 1 antipsychotic.

Our review of the literature on using antipsychotics for MDD suggests that the lower boundary of the antipsychotic PORT dose provides a reasonable approximation of the doses typically used for augmentation treatment in MDD. Even though the FDA has not specified approved MDD doses for any drugs other than aripiprazole and research is thus far inadequate to identify appropriate doses for each SGA, we use the lower end of the antipsychotic range as a rough benchmark separating appropriate MDD doses from conventional antipsychotic dosing.

Data describing patient characteristics, such as age, income, gender, race, ethnicity, receipt of VA disability compensation, comorbid psychiatric diagnoses, and both outpatient and inpatient service utilization, were obtained from VA workload databases. *International Classification of Diseases, Ninth Revision* (ICD-9) codes were used to identify the following non–mutually exclusive comorbid diagnoses: dementia/Alzheimer's disease, psychotic disorders other than schizophrenia spectrum diagnoses and bipolar disorder (ICD 9 codes 297–299, which include paranoid disorders and depressive psychosis), dysthymic disorder, posttraumatic stress disorder (PTSD), anxiety disorders other than PTSD, alcohol abuse/dependence, and drug abuse/dependence.

Diagnostic data from outpatient records from the previous 2 years (fiscal year 2005 and fiscal year 2006) were used to create a proxy measure of chronicity in the form of 2 dichotomous variables indicating whether each patient had also received a diagnosis of MDD in 1 or more of these 2 prior years.

We also examined facility characteristics of VA medical centers. These include the size of the medical center as reflected by the number of full-time employees, emphasis on mental health as reflected by the percentage of the medical center budget allocated for mental health, and academic emphasis as reflected by the proportion of mental health expenditures devoted to research and education.

Analyses

First, descriptive data on the sample and the frequency with which veterans in different age groups received antipsychotic medications, and the frequency with which veterans received these medications at the suggested MDD doses, are presented. We then used bivariate χ^2 and t tests to compare the characteristics of veterans who received antipsychotic medications and those who did not. Next, we used generalized estimating equations[28] to identify veteran characteristics, measures of service use, and VA medical center characteristics that were independently associated with dichotomous dependent variables representing receipt of a prescription for any antipsychotic medications and, among users, with receipt of appropriate MDD doses. Generalized estimating equations are used instead of logistic regression to adjust the standard errors of the parameter estimates for the correlations between observations from the same medical center, especially facility characteristics that are unique to each medical center.

Given the very large sample size, trivial effects could be statistically significant at conventional α levels. We thus opted for a more conservative criterion for meaningful effects—an increase or decrease of 10% in the odds of prescription of an antipsychotic or, among those prescribed an antipsychotic, in the odds of receiving an appropriate MDD dose, or a p value of $< .001$ for continuous independent measures.

RESULTS

Altogether 191,522 VA patients received a diagnosis of MDD with no comorbid diagnosis of bipolar or schizophrenic disorders in fiscal year 2007, about 13% of all VA patients who received a psychiatric diagnosis (unpublished data from the VA Northeast Program Evaluation Center). Of these patients, 39,441 (20.6%) received antipsychotic medications and of these, 22,412 (56.8%) received doses below those recommended for schizophrenia. The most frequently used medication was quetiapine (48.6%), followed by risperidone (23.2%) and olanzapine (7.6%). Mean doses and interquartile ranges are presented in Table 1.

Altogether 176,717 (92.3%) received treatment in a specialty mental health program and 14,805 (7.7%) received service exclusively in medical-surgical clinics. These patients had a mean (SD) age of 55.1 (13.3) years and a mean (SD) income of $32,500 ($43,843), and 87.0% were male, 61.6% were white, 7.6% were black, 42.7% were classified as unknown race, and 3.7% were Hispanic (Table 2).

Table 1. Rate of Use and Dose of Antipsychotic Medications Among U.S. Veterans Diagnosed With Major Depressive Disorder (MDD) (N = 39,441)

Medication	Percent of Use	Taking MDD Dose, %	Mean Dose, mg/day	Median Dose, mg/day	Interquartile Range (25%–75%), mg/day	Recommended Doses for Schizophrenia, mg/day
Conventional antipsychotics	8.50	83.78				
Second-generation antipsychotics	91.94	53.58				
Quetiapine	48.61	67.74	145.56	100	50–200	150–750
Risperidone	23.21	50.93	1.99	1.50	1–2.5	2–6
Aripiprazole	9.14	26.55	14.30	10.0	7.5–20	10–30
Olanzapine	7.58	15.16	10.68	10.0	5–15	5–20
Ziprasidone	3.91	8.63	97.58	80.0	40–140	40–160
Clozapine	0.01	0.00	491.67	500	400–575	150–600

Bivariate Comparison

As compared to patients who did not receive a prescription for antipsychotic medications, a greater percentage of those who did receive medications were treated in specialty mental health clinics (91.10% vs. 97.70%, respectively, $p < .0001$), had been admitted to a psychiatric inpatient unit (14.5% vs. 5.7%, $p < .0001$), and had a greater mean number of mental health outpatient visits (16.4 vs. 9.5 visits, $p < .0001$) (Table 2). They were also more likely to have been diagnosed with "other" psychotic disorders (i.e., other than schizophrenia or bipolar disorder), comorbid Alzheimer's disease or other organic brain syndromes, PTSD, alcohol abuse, or drug abuse and were more likely to have been diagnosed with MDD in fiscal year 2005, 3 years before the current study period ended, but not in fiscal year 2006.

Considering sociodemographic characteristics, veterans who received antipsychotic medications were more likely to be black or Hispanic and to have received a service-connected disability of greater than 50% compared to those who did not receive antipsychotic medications.

Multivariable Analysis

Sociodemographic characteristics. Generalized estimating equations showed that veterans who were aged 65 to 84 years were significantly less likely to receive antipsychotic prescriptions than younger veterans (OR = 0.65 to 0.68; Table 3), and among recipients, older veterans were significantly more likely to receive the proposed MDD dose rather than the higher antipsychotic dose (OR = 2.41 to 1.69; Table 3). Patients 85 years or older were over 3 times more likely to receive antipsychotics at the lower MDD dose.

Male veterans were more likely to receive antipsychotic treatment than female veterans (OR = 1.25), and among recipients, they were less likely to receive the suggested MDD dose (OR = 0.76). Blacks had a higher likelihood of receiving antipsychotic medications (OR = 1.11) and less likelihood of receiving these medications only at the lower MDD doses (OR = 0.91) (Table 3).

Diagnostic characteristics. The comorbid diagnoses of "other" psychotic disorders was by far the strongest clinical predictor of receiving antipsychotic medications in this sample (OR = 6.7), followed by Alzheimer's disease or other organic brain syndromes (OR = 2.4). Patients with a comorbid diagnosis of PTSD were also more than twice as likely to be treated with antipsychotic medications. Comorbid diagnosis of dysthymic disorder was a significant predictor of receiving the MDD dose while "other" psychoses and PTSD were associated with reduced likelihood of using MDD doses. Receipt of a diagnosis of MDD for 2 and 3 years prior to the fiscal year 2007 study period was associated with a 48% and 98% increased likelihood of receiving antipsychotics, respectively, as well as with a decreased likelihood of receiving these medications at a MDD dose (OR = 0.80 and 0.63, respectively) (Table 3).

Service utilization. Both treatment in a specialty mental health clinic and a history of psychiatric hospitalization were strong predictors of receiving antipsychotics (OR = 2.98 and 2.08, respectively), but hospitalized patients were less likely to receive these drugs at MDD doses (OR = 0.76) (Table 3).

Facility characteristics. Increased emphasis on mental health, as measured by the percent of the facility budget allocated to mental health care, was the only significant facility-level predictor and was associated with decreased likelihood of prescribing antipsychotics for MDD. None of the facility characteristics were significantly associated with prescription at or below the recommended antipsychotic dose.

To summarize, greater likelihood of receiving antipsychotics was associated with younger age; male gender; psychiatric comorbidities, especially "other" psychotic disorders; duration of diagnosed illness; and more intensive mental health service use. Among those who were prescribed such drugs, these characteristics were all associated with greater likelihood of receiving antipsychotics at conventional antipsychotic doses.

DISCUSSION

This study examined data on antipsychotic prescribing for all veterans who received a diagnosis of MDD, excluding comorbid diagnoses of schizophrenia, schizoaffective disorder, or bipolar disorder, nationally in the VA

Table 2. Sociodemographic and Clinical Characteristics of U.S. Veterans With Major Depressive Disorder (N = 191,522) and Medical Center Characteristics[a]

Characteristic	Prescribed Antipsychotics (N = 39,441 [20.6%])	Not Prescribed Antipsychotics (N = 152,081 [79.4%])
Sociodemographic characteristics		
Sex		
Male	88.65	86.63
Female	11.35	13.37
Age		
Mean (SD), y	54.30 (12.13)	55.34 (13.52)
≥ 85 y	1.12	1.45
75–84 y	5.26	7.48
65–74 y	6.91	10.39
55–64 y	41.82	39.03
45–54 y	26.94	22.92
Race and ethnicity		
White	61.63	66.63
Black	9.72	7.03
Unknown race	48.44	41.15
Hispanic	5.53	3.26
Service-connected disability > 50%	39.64	29.94
Service-connected disability ≤ 50%	15.91	18.42
Income, mean (SD)	$21,230 (31,169)	$24,089 (46,552)
Clinical characteristics		
Diagnosis of MDD for 2 years	23.87	24.44
Diagnosis of MDD for 3 years	47.88	37.04
Other psychotic disorders	9.00	1.30
Posttraumatic stress disorder	51.02	32.08
Anxiety disorder	29.77	24.60
Dysthymic disorder	48.67	46.67
Alcohol abuse	21.17	14.93
Drug abuse	18.00	10.55
Alzheimer's disease/organic brain syndrome	2.23	1.20
Service utilization		
Any inpatient mental health treatment	14.50	5.65
Mental health outpatient visits, mean (SD)	16.39 (32.67)	9.53 (22.84)
Treated in mental health specialty clinic	97.70	91.10
Medical center characteristics		
VAMC size (total number of employees), mean (SD)	1965 (935)	1987 (958)
MH emphasis (percent of VAMC budget for MH expenditure), mean (SD)	11.4 (6.0)	11.6 (6.0)
Academic emphasis (percent of MH expenditures for research or education), mean (SD)	8.9 (8.1)	8.9 (7.7)

[a]Values expressed as percent except where noted.
Abbreviations: MDD = major depressive disorder, MH = mental health, VAMC = U.S. Department of Veterans Affairs medical center.

Table 3. Generalized Estimating Equations Analysis of Sociodemographic and Diagnostic Predictors of Receiving an Antipsychotic and, Among Those Receiving Antipsychotics, of Receiving Suggested MDD Dose

Variable	Any Antipsychotic (N = 39,441), Odds Ratio	Low Dose Antipsychotic (N = 22,412), Odds Ratio
Sociodemographic characteristics		
Male gender	1.25**	0.76**
Age (per 10-year interval)		
≥ 85 y	0.68	3.12**
75–84 y	0.65**	2.41**
65–74 y	0.68**	1.69**
55–64 y	0.88	1.15**
45–54 y	1.11	0.94
Black	1.11	0.91
Unknown race	0.88**	1.10**
Hispanic	1.66	1.01
Service-connected disability > 50%	1.14**	0.94
Service-connected disability ≤ 50%	0.90**	1.12**
Clinical characteristics		
Diagnosis of MDD for 2 years	1.48**	0.80**
Diagnosis of MDD for 3 years	1.98**	0.63**
Other psychotic disorders	6.70**	0.51**
PTSD	2.03**	0.89**
Anxiety disorder other than PTSD	1.21**	1.07
Dysthymia	1.07	1.16**
Alcohol abuse	1.03	0.97
Drug abuse	1.21**	0.95
Alzheimer's disease/organic brain syndrome	2.37**	1.00
Treatment characteristics		
Mental health inpatient	2.08**	0.76**
Mental health outpatient (per 10 visits)	1.03	1.00
Treatment in a mental health specialty clinic	2.98**	0.84*
Medical center characteristics		
VAMC size	1.00	1.00
MH emphasis (10%)	0.88*	1.00
Academic emphasis (10%)	1.04	0.99

*p < .01.
**p < .001.
Abbreviations: MDD = major depressive disorder, MH = mental health, PTSD = posttraumatic stress disorder, VAMC = U.S. Department of Veterans Affairs medical center.

health care system in fiscal year 2007. These medications were used to treat 20.6% of MDD patients. Among those who received these medications, 56.8% were prescribed doses presumed appropriate for MDD (i.e., lower than the PORT-recommended antipsychotic doses), while 43.2% received doses within the PORT-recommended range for the treatment of schizophrenia. Only 9% of veterans who received an antipsychotic prescription were diagnosed with "other" psychotic disorders. Thus, even prior to FDA approval of the first SGA as an augmenting agent to antidepressants, antipsychotics were commonly used in the treatment of MDD, in most instances at doses appropriate for patients with schizophrenia.

The strongest predictors of antipsychotic medication use were general indicators of clinical severity, such as use of more outpatient mental health services, inpatient psychiatric hospitalization, chronicity or presumably inadequate response to treatment (i.e., diagnosis of MDD 2 or 3 years prior to the study period), receipt of VA disability compensation, or a diagnosis of other psychosis (which includes both paranoid disorders and depressive psychosis),

Alzheimer's disease, or PTSD. There was also a modest positive association of antipsychotic prescription and drug abuse/dependence. Second-generation antipsychotics may reduce substance use,[29] and perhaps that strategy is being used in the treatment of patients with MDD. Substance abuse was previously found to be a modest predictor of using antipsychotics in a sample of patients with PTSD.[30]

Only 7.7% of patients diagnosed with MDD in this sample were treated exclusively in primary care or medical-surgical specialty clinics. Those treated in specialty mental health clinics were more than twice as likely to receive antipsychotic medications and were significantly less likely to receive these medications at lower MDD doses. This finding likely reflects greater symptom severity, possibly associated with psychotic features, chronicity, or unresponsiveness to antidepressants of patients treated in specialty mental health clinics and the greater comfort of specialty clinic prescribers with off-label use of antipsychotics.

While it is impossible to determine from administrative data the clinical rationale for the off-label prescription of antipsychotic medications, a likely explanation is that off-label use of these drugs was intended to address unresponsive or psychotic symptoms of MDD or to target symptoms associated with other disorders, such as flashbacks or sleep disturbances in PTSD, based on scattered research reports.[31] Without more detailed review of the medical records than is possible here, the precise rationale for these prescriptions cannot be determined. We can only conclude that there seems to have been modest rates of off-label use of antipsychotics to treat MDD even before the first SGA received FDA approval for this disorder.

While focused on the overall rates of treatment of MDD with antipsychotics in the VA health care system, we also examined multivariate analyses for age trends across 5 age cohorts: 45–54, 55–64, 65–74, 75–84, and ≥ 85 years, with veterans younger than 45 years as the reference group. The odds of receiving antipsychotics decreased significantly and consistently between ages 65 and 84. Reciprocally, the likelihood of receiving antipsychotics at doses appropriate for MDD, rather than at higher doses appropriate for schizophrenia, increased significantly in patients over 55 years of age. This may reflect appropriate caution in consideration of side effects and risks[32,33] and age-related medical comorbidities with the associated increase in number of prescription and nonprescription medications.[34]

The use of lower doses in elderly veterans may also reflect general awareness of the decreased drug clearance due to hepatic blood flow, hepatic mass, and protein binding changes in older patients,[35] and reluctance to expose older patients to off-label medication use. It may also reflect lower symptom levels in the elderly or some hesitancy to aggressively treat complex or refractory illness. The impact of age-related medical disorders on the psychopharmacotherapy for the elderly is complex. Even when adequate treatment is provided, comorbid medical conditions are associated with poorer responses and may require, in some cases, more aggressive treatment.[36,37] Further research is needed to evaluate augmentation strategies in older patients and to establish clinical protocols for safe administration of higher doses when indicated.

The most important limitation of this study is the exclusive reliance on diagnoses recorded in administrative VA data files, and especially on unvalidated and possibly unrecorded diagnoses. Some apparently off-label prescribing may reflect failure to enter all relevant diagnostic codes (e.g., major depression with psychotic features) or use of these medications for symptomatic treatment of insomnia, anxiety, agitation, or violent behavior. In addition, appropriate dosing of antipsychotics for MDD has been established by the FDA only for aripiprazole. The "appropriate" MDD dose used for reference in this study, while based on published research, is not based on FDA-approved dose recommendations.

This examination of the use of antipsychotics in MDD nationally in the VA health care system showed the level of use to be about one fifth of MDD patients without comorbid schizophrenia or bipolar disorder. Although we do not know the prevalence of MDD that was unresponsive to antidepressants (in this sample), the rate of comorbid psychotic disorders exclusive of schizophrenia or bipolar disorder was only about 9%. When dosing was considered, over half of those receiving these medications received them at higher, schizophrenia-recommended dose levels. While there have been reports of at least some potential short-term benefit of this augmentation strategy, special caution is indicated in long-term use since studies have clearly shown increased risk of heart disease among people with MDD,[20,21,38,39] a risk that may be further increased by the additional metabolic risk associated with olanzapine and clozapine, and to a lesser extent with quetiapine and risperidone.[22,23] Expanded use of these drugs in MDD could also result in increased drug costs, although the lower dosing of antipsychotics in MDD may moderate this effect.

Future research comparing the long-term safety, efficacy, and cost-effectiveness of antipsychotic augmentation in MDD, as compared to other possible strategies, and to antidepressants alone, is urgently needed, particularly in the treatment of geriatric patients and those at high metabolic risk.

Drug names: aripiprazole (Abilify), clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), ziprasidone (Geodon).

REFERENCES

1. US Food and Drug Administration approves Abilify (aripiprazole) as the first medication for add-on treatment of major depressive disorder (MDD) [news release]. Bristol-Myers Squibb; November 20, 2007. Available at: http://newsroom.bms.com/

article_display.cfm?article_id=5222. Accessibility verified Jan 21, 2009
2. Mahmoud RA, Pandina GJ, Turkoz I, et al. Risperidone for treatment-refractory major depressive disorder: a randomized trial. Ann Intern Med 2007;147(9):593–602
3. World Health Organization. Revised global burden of disease (GBD) 2002 estimates. 2005. World Health Organization Web site. Available at: http://www.who.int/healthinfo/global_burden_disease/estimates_regional_2002_revised/en/index.html. Accessibility verified Feb 23, 2009
4. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289(23):3095–3105
5. Johnson J, Horwath E, Weissman MM. The validity of major depression with psychotic features based on a community study. Arch Gen Psychiatry 1991;48(12):1075–1081
6. Ohayon MM, Schatzberg AF. Prevalence of depressive episodes with psychotic features in the general population. Am J Psychiatry 2002; 159(11):1855–1861
7. Rothschild AJ, et al. Challenges in differentiating and diagnosing psychotic depression. Psychiatr Ann 2006;36(1):40–46
8. Trivedi MH. Treatment-resistant depression: new therapies on the horizon. Ann Clin Psychiatry 2003;15(1):59–70
9. O'Reardon JP, Amsterdam JD. Treatment-resistant depression: progress and limitations. Psychiatr Ann 1998;28:633–640
10. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2007;68(6):843–853
11. Shekelle P, Maglione M, Bagley S, et al. Comparative effectiveness of off-label use of atypical antipsychotics. In: Comparative Effectiveness Review No. 6. Rockville, MD: Agency for Healthcare Research and Quality, US Dept of Health and Human Services. January 2007. AHRQ publication 07-EHC003-EF. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessibility verified Jan 26, 2009
12. Worthington JJ 3rd, Kinrys G, Wygant LE, et al. Aripiprazole as an augmentor of selective serotonin reuptake inhibitors in depression and anxiety disorder patients. Int Clin Psychopharmacol 2005;20(1):9–11
13. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001; 158(1):131–134
14. Papakostas GI, Petersen TJ, Nierenberg AA, et al. Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. J Clin Psychiatry 2004;65(2):217–221
15. Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. J Clin Psychiatry 1999; 60(4):256–259
16. Adson DE, Kushner MG, Eiben KM, et al. Preliminary experience with adjunctive quetiapine in patients receiving selective serotonin reuptake inhibitors. Depress Anxiety 2004;19(2):121–126
17. Nemeroff CB, Gharabawi GM, Canuso CM, et al. Augmentation with risperidone in chronic resistant depression: a double-blind placebo controlled maintenance trial. Neuropsychopharmacology 2004;29 (suppl 1):S159
18. Dube S, Anderson SW, Paul S. Meta-analysis of olanzapine-fluoxetine use in treatment-resistant depression. Int J Neuropsychopharmacol 2002;5(suppl 1):105–106
19. Lehman AF, Kreyenbuhl J, Buchanan RW, et al. The Schizophrenia Patient Outcomes Research Team (PORT): updated treatment recommendations 2003. Schizophr Bull 2004;30(2):193–217
20. Frasure-Smith N, Lesperance F. Reflections on depression as a cardiac risk factor. Psychosom Med 2005 May–Jun;67(suppl 1):S19–S25
21. Whooley MA. Depression and cardiovascular disease: healing the broken-hearted. JAMA 2006;295(24):2874–2881
22. Newcomer JW. Metabolic considerations in the use of antipsychotic medications: a review of recent evidence. J Clin Psychiatry 2007;68 (suppl 1):20–27
23. Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. J Clin Psychiatry 2007;68(suppl 4):8–13
24. Fava M. Weight gain and antidepressants. J Clin Psychiatry 2000;61(suppl 11):37–41
25. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry 2001;62(suppl 7):22–31
26. Taylor DM, McAskill R. Atypical antipsychotics and weight gain: a systematic review. Acta Psychiatr Scand 2000;101(6):416–432
27. Greenberg G, Rosenheck RA. National Mental Health Program Performance Monitoring System: Fiscal Year 2006 Report. West Haven, Conn: Northeast Program Evaluation Center; 2007
28. Laing KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22
29. Green AI, Noordsy DL, Brunette MF, et al. Substance abuse and schizophrenia: pharmacotherapeutic intervention. J Subst Abuse Treat 2008;34(1):61–71
30. Mohamed S, Rosenheck RA. Pharmacotherapy of PTSD in the US Department of Veterans Affairs: diagnostic and symptom-guided drug selection. J Clin Psychiatry 2008;69(6):959–965
31. Bartzokis G, Lu PH, Turner J, et al. Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. Biol Psychiatry 2005;57(5):474–479
32. Gill SS, Bronskill SE, Normand SL, et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 2007;146(11):775–786
33. Schneeweiss S, Setoguchi S, Brookhart A, et al. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ 2007;176(5):627–632
34. Chrischilles EA, Foley DJ, Wallace RB, et al. Use of medications by persons 65 and over: data from the established populations for epidemiologic studies of the elderly. J Gerontol 1992;47(5):M137–M144
35. Le Couteur DG, McLean AJ. The aging liver: drug clearance and an oxygen diffusion barrier hypothesis. Clin Pharmacokinet 1998;34(5): 359–373
36. Katz IR, Simpson GM, Curlik SM, et al. Pharmacologic treatment of major depression for elderly patients in residential care settings. J Clin Psychiatry 1990;51(7, suppl):41–47; discussion 48
37. Popkin MK, Callies AL, Mackenzie TB. The outcome of antidepressant use in the medically ill. Arch Gen Psychiatry 1985;42(12):1160–1163
38. Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. Circulation 1996;93(11):1976–1980
39. Pratt LA, Ford DE, Crum RM, et al. Depression, psychotropic medication, and risk of myocardial infarction: prospective data from the Baltimore ECA follow-up. Circulation 1996;94(12):3123–3129